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MEMORANDUM

SUBJECT: *OXYDEMETON-METHYL (ODM)* - Report of the FQPA Safety Factor Committee

The FQPA safety factor, and basis and rationale for the recommendation in this report supercedes that previously reported for ODM in the FQPA SAFETY FACTOR RECOMMENDATIONS FOR THE ORGANOPHOSPHATES dated August 6, 1998.

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THROUGH: Ed Zager, Chairman
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PC Code: 058702

The FQPA Safety Factor Committee met on July 12, 1999 to reevaluate the hazard and exposure data for ODM considering a recently reviewed toxicokinetic study submitted for this organophosphate. Based on these new data, the Committee recommended that the FQPA safety factor (as required by Food Quality Protection Act of August 3, 1996) be removed in assessing the risk posed by this chemical. The FQPA safety factor, and the basis and rationale for the recommendation in this report supercedes that previously reported for ODM in the *FQPA SAFETY FACTOR RECOMMENDATIONS FOR THE ORGANOPHOSPHATES* dated August 6, 1998.

I. HAZARD ASSESSMENT

A. Adequacy of Toxicology Database

On July 8, 1999, the HIARC evaluated the merit of a toxicokinetic study in the rat (00152368), and the impact of this study on the acceptability of a previously submitted and reviewed *in vivo* alkaline elution assay in the rat (43776101). The alkaline elution assay was previously graded as unacceptable because there was concern that exposure to oxydemeton methyl may not have had enough time (4 hours) to allow for sufficient interaction with the target organ (testes).

The Registrant has submitted a toxicokinetic study with oxydemeton methyl in the rat in which the blood and tissue distribution (including the testes) was measured over a time course of 20 minutes to 10 days post-dosing. The toxicokinetic study clearly demonstrated that after 4 hours, oxydemeton methyl had enough time to distribute throughout the body, and that the testes were adequately exposed during this time. Because there was no longer any concern about the adequacy of the time used in the alkaline elution assay, the HIARC agreed that the *in vivo* alkaline elution assay in the rat was acceptable.

The acceptability of the alkaline elution assay, in conjunction with the negative results of this assay as well as the negative findings of the dominant lethal assays, lowered the concern for heritable effects from exposure to ODM and obliged the HIARC to evaluate the results of the mouse spot test critically. The primary function of the mouse spot test is as a carcinogenesis screening tool. Although ODM was positive in this test system, it was negative in other *in vivo* assays with somatic cells. In addition, ODM was shown to be non-carcinogenic in CD-1 mice and Fischer 344 rats.

Based on a weight-of-evidence re-evaluation, the HIARC concluded that the genetic concern resulting from exposure to ODM have been addressed. The requirement for the mouse specific locus test, which evaluates adverse effect on germinal cells, is revoked. Therefore, the toxicology database for ODM is now complete (*MEMORANDUM*: R. Fricke to A. Neilsen dated July 21, 1999).

B. Evaluation of Neurotoxicity

ODM is a neurotoxic organophosphate. Administration to various species (rat, mouse, dog, monkey) results in progressive ChE inhibition in the plasma, erythrocyte, and brain. Adequate characterization of the ChE inhibition response has been conducted.

Delayed neuropathy (axonal degeneration) was observed following a single dose in the acute delayed neurotoxicity study with ODM in hens but no neuropathology was seen following repeated dose in hens. No evidence of neuropathology was seen following single or repeated dosing in rats.

C. Developmental Toxicity

No evidence of developmental anomalies, including abnormalities in the development of the fetal nervous system, were observed in the prenatal developmental toxicity studies in either rats or rabbits. Although an apparent treatment-related increase of the brain malformation hypoplasia of the telencephalon was noted in a developmental toxicity study in Long Evans rats, these results were found to be equivocal because of the high historical incidence of brain malformations in this strain at the time of study conduct.

D. Reproductive Toxicity

In the two-generation reproduction studies in the rat, reproductive toxicity was seen at doses which were the same or higher than maternally toxic doses. Additionally, no clinical evidence suggestive of neurotoxicity was observed grossly in pups, which had been administered ODM *in utero* and during early and late postnatal development, generally mediated by maternal dietary exposure, but also available in the diet to late lactation pups.

E. Determination of Requirement of Developmental Neurotoxicity Study

The HIARC determined that a developmental neurotoxicity study in rats is **not** required for ODM.

F. Determination of Susceptibility

Based on the weight-of-the-evidence of all available studies, the HIARC concluded that there was no increased susceptibility to rat and rabbit fetuses following *in utero* and/or post natal exposure to ODM. In the prenatal developmental toxicity studies in rats and rabbits, no evidence of developmental toxicity was seen even in the presence of maternal toxicity. In the two generation reproduction studies in the rat, reproductive toxicity was seen at doses which were the same as or higher than maternally toxic doses.

G. Data Gaps

Based on the recently submitted toxicokinetic data and weight-of-evidence re-evaluation of the genetic concerns resulting from exposure to ODM, the HIARC revoked the requirement for the mouse specific locus test which was previously identified as a data gap (Revised Report of the HIARC dated May 7, 1998; HED Doc. No. 012606). Therefore, the toxicity data base for ODM is now complete.

II. EXPOSURE ASSESSMENT AND RISK CHARACTERIZATION

(Correspondence: P. Deschamp to B. Tarplee dated July 8, 1999)

A. Dietary (Food) Exposure Considerations

Tolerances are established for the combined residues of the insecticide, oxydemeton-methyl, and its cholinesterase-inhibiting metabolites in/on various raw agricultural plant and animal commodities [40 CFR §180.330(a) and (b)] and processed feed commodities [40 CFR §186.3050] at levels ranging from 0.1 ppm to 12.5 ppm. For purposes of tolerance reassessment, ODM residues of concern in plants are ODM and oxydemeton-methyl sulfone (ODMS) and animal commodities have been determined to include ODM *per se* (HED Metabolism Committee (3/6/97)). There are Codex MRL's for ODM on most all the commodities for which there are reassessed tolerances.

ODM is used on crops considered to be highly consumed by infants and children such as pears, orange, potato, squash, sweet corn, sugar beet (sugar), green bean, lettuce, peas, cantaloupe, onion.

Field trial data are available for all crops on which ODM is used. There are also monitoring data (both PDP and FDA) available for many commodities. Monitoring data over many years show no detectable residues of ODM on foods as consumed, indicating that the residues are likely removed during the routine preparation such as washing, peeling, and cooking. This assumption is substantiated by results of cooking study submitted by the registrant which showed residue reduction of approximately 80%. Information on percent of the crop treated with ODM is also available (BEAD report dated 11/10/98 entitled *Quantitative Usage Analysis for Oxydemeton-methyl*).

Dietary food exposure analyses were performed to estimate the dietary risk resulting from the residues of oxydemeton-methyl on foods. These analyses combine pesticide residue data with food consumption data to estimate dietary (food only) exposure. Both the acute and chronic dietary food exposure analyses are highly refined using anticipated residue estimates from monitoring data and field trial studies as well as percent crop treated data. The result is a more realistic estimate of the dietary exposure expected from ODM residues in food commodities.

B. Dietary (Drinking Water) Exposure Considerations

(Correspondence: J. Breithaupt to B. Tarplee dated July 6, 1999)

The environmental fate database for Oxydemeton-methyl (ODM) is incomplete. However, existing fate data indicate that the parent compound, ODM, or its metabolite of toxicological concern, ODMS, are not expected to persist in surface water or expected to leach to ground water.

Monitoring data for residues of oxydemeton-methyl in ground and surface water are limited. Therefore, modeling was performed to calculate estimated environmental

concentrations (EECs) using SCI-GROW Tier 1 for ground water; and GENEEC and PRZM/EXAMS for surface water. These models generate upper-bound estimates of the concentrations that might be found in surface and ground water due to use of oxydemeton-methyl based on simulations performed using the maximum application rates of 1.50-3.76 lb/ai/A applied three times/year with 7-14 day intervals between applications.

The limited monitoring data indicate that ODM has not been detected in ground and surface water samples at a detection limits of 0.1 and 0.5 ppb. The estimated environmental concentrations (EECs) for ground and surface water are equal to or greater than these detection limits, thus indicating that the models are not likely to underestimate the potential for ODM residues in drinking water.

C. Residential Exposure Considerations

Oxydemeton-methyl is not currently registered for residential use.

III. SAFETY FACTOR RECOMMENDATION AND RATIONALE

A. Recommendation of the Factor

The Committee recommended that the FQPA safety factor for protection of infants and children (as required by FQPA) should be removed (1x) for ODM.

B. Rationale for Removal of the FQPA Safety Factor

The FQPA SFC concluded that a safety factor is not required for the following reasons:

- ▶ Based on the recently submitted toxicokinetic data and a weight-of-evidence re-evaluation of the genetic concerns resulting from exposure to ODM, the HIARC revoked the requirement for the mouse specific locus test which was previously identified as a data gap.
- ▶ The toxicity data base for ODM is now complete.
- ▶ The HIARC concluded that the genetic concerns resulting from exposure to ODM have been addressed;
- ▶ There was no evidence of developmental effects being produced in fetuses at lower doses as compared to maternal animals nor was there evidence of an increase in severity of effects at or below maternally toxic doses following *in utero* exposure in the prenatal developmental toxicity studies in rats and rabbits;
- ▶ In the pre/post natal two-generation reproduction study in rats, there was no evidence of enhanced susceptibility in pups when compared to parental animals (i.e., effects noted in offspring occurred at maternally toxic doses or higher);
- ▶ There was no evidence of abnormalities in the development of the fetal nervous system in the pre/post natal studies submitted to the Agency; and
- ▶ Adequate actual data, surrogate data, and/or modeling outputs are available to satisfactorily assess dietary (food) exposure and to provide a screening level drinking water exposure assessment.